



Review

Rethinking the benefits and costs of childhood vaccination: The example of the *Haemophilus influenzae* type b vaccine[☆]

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ABSTRACT

Economic evaluations of health interventions, such as vaccinations, are important tools for informing health policy. Approaching the analysis from the appropriate perspective is critical to ensuring the validity of evaluation results for particular policy decisions. Using the example of cost–benefit analysis (CBA) of *Haemophilus influenzae* type b (Hib) vaccination, we demonstrate that past economic evaluations have mostly adopted narrow evaluation perspectives, focusing primarily on health gains, health-care cost savings, and reductions in the time costs of caring, while usually ignoring other important benefits including outcome-related productivity gains (improved economic productivity due to prevention of mental and physical disabilities), behavior-related productivity gains (economic growth due to fertility reductions as vaccination improves child survival), and community externalities (herd immunity and prevention of antibiotic resistance). We further show that potential cost reductions that could be attained through changes in the delivery of the Hib vaccine have also generally been ignored in economic evaluations. Future economic evaluations of childhood vaccinations should take full account of benefits and costs, so that policymakers have sufficient information to make well-informed decisions on vaccination implementation.

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1. Introduction

Childhood vaccination programs have had a dramatic impact on child morbidity and mortality worldwide. A universal effort to extend vaccination coverage to all children began in 1974, when the World Health Organization (WHO) founded the Expanded Program on Immunization (EPI). This initiative helped countries establish the infrastructure needed to deliver a standard vaccination package (Original EPI in Table 1), which in 1974 included the diphtheria–tetanus–pertussis (DTP) vaccine, measles-containing vaccine (MCV), polio vaccine (Pol), and Bacillus Calmette–Guérin (BCG) vaccine. Over time, other vaccines have been added to national EPI packages in some countries (Later-stage EPI in Table 1), including those against *Haemophilus influenzae* type b (Hib), yellow fever (YF), and hepatitis B (HepB) [1].

Despite the longstanding availability of EPI vaccines and national health policies aiming at universal or near universal coverage [2], actual coverage is widely incomplete. For instance, Lim et al. estimated that, in 2006, 26% of children younger than one year of age worldwide had not received the third dose of the DTP vaccination series (DTP3) [3]. DTP3 coverage is commonly used as an indicator to assess the performance of national vaccination systems because it captures a system's capacity to repeatedly vaccinate the same individual and to record vaccine doses. The deficits in DTP3 coverage discussed by Lim et al. thus suggest that millions of children are not receiving the full course of recommended vaccines [3].

Incomplete vaccination coverage, in turn, leads to large numbers of avoidable child deaths. Currently, the three vaccine-preventable diseases responsible for the highest mortality burdens in children are pneumococcal disease, rotavirus infection, and Hib infection, which in 2002 were responsible, respectively, for an estimated 716,000, 402,000, and 386,000 deaths in children under five years of age (Table 1) [4]. Those children who do not die from vaccine-preventable diseases may suffer debilitating sequelae. For example, Hib infection and pneumococcal disease can cause bacterial meningitis, which may lead to severe neurological conditions such as deafness, blindness, or intellectual impairment.

In deciding whether to finance a health-care intervention, decision-makers should consider not only the effects of the intervention, but also the costs. Cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA) are the most common approaches to systematically compare the costs and effects of health-care interventions. CEA evaluates the health effectiveness of an intervention relative to the costs. In CEA, effectiveness is measured either in natural units of health, such as cases of a disease averted or deaths averted, or in units of a composite health index that combines information on length and quality of life, such as reduction in disability-adjusted life years (DALYs).¹ In contrast, CBA compares monetary measures of intervention benefits to costs. Below, we argue that economic evaluations of vaccination have traditionally adopted a *narrow perspective*, considering only some categories of vaccination effects and failing to account for changes in vaccine costs that can be achieved by combining several vaccines into a single delivery system.

Such a narrow perspective can lead to an underestimation of the benefits of a vaccination and to an overestimation of its costs, resulting in ill-founded decisions. A broad perspective in CBA, CEA, or other types of economic evaluation of vaccinations should thus replace the narrow perspective. We have chosen the Hib vaccine as an example to make this case. By 2008, the Hib vaccine had been introduced into national routine immunization schedules in 136

WHO Member States—however, Hib3 vaccination coverage across these 136 countries was estimated at merely 28% in the same year (Table 1) [6].

Hib is among the vaccinations that could prevent the largest number of deaths in children under five years of age (Table 1). Unlike the two other vaccines that could, on their own, prevent even larger numbers of deaths in children in this age group (the vaccine against pneumococcal disease and the vaccine against rotavirus infection), Hib vaccine can be combined with DTP vaccine to be delivered as a multivalent formulation in a single injection (DTP–Hib). Vaccination with DTP–Hib could prevent 789,000 deaths annually, i.e., more deaths than either the rotavirus vaccination or the pneumococcal vaccination could prevent.

2. The *Haemophilus influenzae* type b vaccine

Infection with Hib can give rise to different diseases and disease sequelae. Humans are the only known reservoir of Hib. Person-to-person transmission of the bacteria occurs via respiratory droplets. In some cases, after droplet contact the bacteria colonize the nasopharyngeal mucosa and enter the bloodstream causing invasive disease (including meningitis, pneumonia, and epiglottitis), with high rates of both mortality and long-term sequelae.

In 1985, a polysaccharide vaccine against Hib was licensed in the United States. However, the vaccine displayed limited immunogenicity among children under two years of age and was not effective in reducing the incidence of infection. It was later removed from the market [8]. In 1987, the United States licensed a protein-conjugated Hib vaccine [8]. Many studies have demonstrated the success of the conjugate vaccine in reducing child morbidity and mortality. Following routine use of the conjugate Hib vaccine in the US since 1990, the national incidence of invasive Hib disease decreased from pre-vaccination levels of 41 per 100,000 children per year (in 1987) to approximately 1 case per 100,000 children per year (in 1997) [9].²

Success of the Hib vaccine is not limited to developed countries. A 2006 study in Kenya showed that the vaccination reduced the incidence of invasive Hib disease by 88% within three years and prevented approximately 3,370 Kenyan children from being hospitalized in 2005 [10]. A 2007 study in Bangladesh found that routine Hib vaccination of infants could prevent over one third of Hib pneumonia cases and approximately 90% of meningitis cases [11]. A 2008 study in Uganda estimated that within four years of the introduction of the Hib vaccine into the national immunization program, the incidence of Hib meningitis declined by 85%. By the fifth year after introduction, the number of cases had fallen to nearly zero [12]. These studies suggest that the Hib vaccine is highly effective at reducing Hib-related morbidity and mortality in a variety of settings. Nevertheless, as stated above, worldwide Hib vaccination coverage stood at only 28% in 2008 (see Table 1).

3. Cost-benefit analysis of Hib vaccination

We performed a comprehensive literature review of CBAs of Hib vaccination in order to assess which benefits and costs have been taken into account in past studies. We chose to review the literature on CBA rather than CEA, despite the more frequent use of the latter in health economics, because our argument that economic evaluations of vaccination have traditionally accounted for too narrow a set of benefits focuses on both health and non-health benefits. In CBA, non-health benefits of vaccinations can be added to health benefits, since both types of benefits are measured in monetary

¹ The subset of cost-effectiveness analysis that uses a composite index of health as a measure of effectiveness is also called cost-utility analysis [5].

² In the following text, the term “Hib vaccine” refers to the conjugate Hib vaccine and the term “Hib vaccination” to the administration of the conjugate Hib vaccine.

Table 1
Vaccination data summary.

Vaccine ^a	Global vaccination coverage ^b (1999) [6]	Global vaccination coverage ^b (2008) [6]	Annual number of deaths worldwide in children under five years due to vaccine-preventable diseases
Original EPI			
Diphtheria–tetanus–pertussis vaccine (DTP3)	72%	82%	5000 diphtheria (2004) [6] 254,000 pertussis (2004) [6] 144,000 tetanus (2004) [6]
Measles-containing vaccine (MCV)	71%	83%	117,000 (2006) [6]
Polio vaccine (Pol3)	73%	82%	NA
Bacillus Calmette–Guérin vaccine (BCG)	79%	89%	NA
Later-stage EPI			
<i>Haemophilus influenzae</i> type b vaccine (Hib3)	8%	28%	386,000 (2002) [7]
Yellow fever vaccine (YF)	21%	50%	15,000 (2002) [6]
Hepatitis B vaccine (HepB3)	18%	69%	NA
New vaccines			
Rotavirus vaccine (Rota2, Rota3)	Not yet introduced in most developing countries	NA	402,000 (2002) [7]
Pneumococcal conjugate vaccine (PCV3)	Not yet introduced in most developing countries	NA	716,000 (2002) [7]

NA = not available.

^a In this column, we show the name of each vaccine and the abbreviation used to denote the last dose of the vaccine in the full vaccination series (excluding booster doses), i.e., DTP3 = third dose of diphtheria–tetanus–pertussis vaccine, MCV = first dose of measles-containing vaccine, Pol3 = third dose of polio vaccine, BCG = first dose of Bacillus Calmette–Guérin vaccine, Hib3 = third dose of *Haemophilus influenzae* type b vaccine, YF = first dose of yellow fever vaccine, HepB3 = third dose of hepatitis B vaccine, Rota2 = second dose of rotavirus vaccine (Rotarix[®]), Rota3 = third dose of rotavirus vaccine (RotaTeq[®]), PCV3 = third dose of pneumococcal conjugate vaccine.

^b The vaccination coverage data are WHO/UNICEF estimates. The denominator used to estimate coverage differs by vaccination. With the exception of YF, the denominators are the “target populations” across all WHO Member States “expected to report” data on the particular vaccination coverage to WHO because they have introduced the relevant vaccine into their routine national immunization schedules. The number of WHO Member States “expected to report” coverage data to WHO was 193 (for DTP3, MCV, Pol3), 160 (for BCG), 177 (for HepB3), and 136 for Hib. In the case of YF, the denominators are the “countries at risk” for yellow fever. While the “target population chosen varies depending on the countries’ policies, the specific vaccine, and the dose for which coverage is being calculated”, in “most instances the target population is the number of children surviving their first year of life”. In the case of BCG, the “target population” is the “national annual number of births” [6].

units. In CEA, on the other hand, health effects are measured either in natural units or in composite indices of health. Hence, non-health benefits cannot be added to the effectiveness side of the analysis. Thus, CBA is the more natural evaluation framework to demonstrate how a broader perspective on vaccination benefits can affect evaluation results.³

We searched medical, economic, and general literature databases (EconLit [14], PubMed [15], Science Citation Index Expanded [16], and JSTOR [17]) to identify CBAs that evaluate Hib vaccination at the national or subnational level. In our search, we found 62 distinct economic evaluation studies of Hib vaccination published from January 1985 through March 2009. After excluding all studies that did not use CBA as an evaluation approach or reported only regional results, 11 studies remained in our final selection for review (see below). Four of the authors (TB, DEB, AF, JO) independently extracted the data from the articles. Discrepant data from the extractions were discussed, and all discrepancies could be resolved. Note that we classified any study as CBA that compared costs and benefits measured in monetary terms, including those studies that compared the cost of a vaccination to only one single benefit, such as health-care cost savings.

4. Rethinking the benefits of vaccination

CBAs of vaccination programs usually account for gains in health, health-care costs, and the time costs of parents taking care of their sick children [13,18]. However, vaccinations are likely to lead to other gains, stemming from the well-known linkages between health and wealth [19,20] and vaccine-related externalities, such as herd effects [21]. Approaching CBA of vaccination from a broad perspective that accounts for all health and non-health gains invites

a new and more comprehensive conceptualization of the benefits of vaccination. Table 2 outlines this approach and illustrates its application for Hib vaccination.⁴

Categories of vaccination benefits that are usually ignored in economic evaluations of vaccinations, such as Hib vaccination, include outcome-related productivity gains, behavior-related productivity gains, and community externalities (see Table 2 for definitions of these types of benefits). Below, we describe examples of these three benefit categories for Hib vaccination.

4.1. Outcome-related productivity gains

Childhood vaccinations may result in outcome-related productivity gains [21] because they protect children’s physical health and ability to achieve their full cognitive potential. Children who are physically and cognitively healthy are more likely to attend school and to attain high education levels. Adults who are physically healthy and well-educated can work more and more productively (see Bloom and Canning [32], Bloom, et al. [20], and Bloom et al. [33] for reviews of the literature on the relationships between health and economic well-being). Hib vaccination can avert long-term neurological sequelae of Hib infection, such as deafness, blindness, mental retardation, epilepsy, and paralysis [27]. Such sequelae can severely affect a child’s ability to attend school and to learn. For example, a longitudinal study in Australia compared outcomes in adolescents who survived a bout of bacterial meningitis, such as Hib meningitis, to outcomes in controls who did not suffer from meningitis. The study revealed “substantial excess risk of intellectual, cognitive, and auditory impairment” and “[c]ontinuing developmental problems of higher order language, organization, problem solving, and central auditory function” in the meningitis survivors, resulting in lower educational achievement and higher risk of behavioral disorders [34]. As cognitive ability and educa-

³ Note that it is theoretically also possible to account for non-health benefits in CEA by expressing them in monetary terms and subtracting them from the cost-side of the analysis. A recent systematic review of CEA of Hib vaccine can be found elsewhere [13].

⁴ Table 2 is a modified version of a table in an earlier publication [21].

Table 2
Types of benefits in economic evaluations of vaccinations.

Perspective	Benefit categories	Definition	Hib-specific examples
Narrow	Health gains	Reduction in mortality through vaccination ^a	Hundreds of thousands of children die each year from Hib disease [22].
	Health-care cost savings	Savings of medical expenditures because vaccination prevents illness episodes	Hib diseases lead to substantial health-care costs [23–25].
	Care-related productivity gains	Savings of parents' productive time because vaccination avoids the need for taking care of a sick child	Parental care of children suffering from Hib disease can contribute substantially to the overall cost of the disease [26].
Broad	Outcome-related productivity gains	Increased productivity because vaccination improves cognition and physical strength, as well as school enrolment, attendance and attainment	Hib meningitis is relatively common and "leaves 15 to 35% of survivors with permanent disabilities such as mental retardation or deafness", which can severely reduce cognition [27].
	Behavior-related productivity gains	Benefits accruing because vaccination improves child health and survival and thereby changes household choices, such as fertility and consumption choices	Hundreds of thousands of children die each year from Hib disease [28].
	Community externalities	Benefits accruing because vaccination improves outcomes among unvaccinated community members	Hib infections are treated with antibiotics, leading to the development of resistance [29]. Hib vaccinations can protect unvaccinated individuals through herd effects [30].

^a The denominator of the cost-effectiveness ratio in CEA is either a measure of mortality (e.g., number of life-years saved), morbidity (e.g., cases of meningitis averted), or mortality and morbidity (e.g., number of DALYs saved). Thus, for CEA the benefits considered in the narrow-perspective category "health gains" should be defined as "reduction in mortality and/or morbidity through vaccination" [21]. In contrast, in CBAs "health gains" in terms of the value of saved life-years are commonly considered (for example, in nine out of 11 studies in Table 3). The value of a life year in CBA usually incorporates pure longevity effects, the productivity gains due to an additional year of life, as well as the value of leisure and joy [31]. In contrast, morbidity reductions are rarely included in CBA (for example, in only one out of the 11 studies in Table 3). If morbidity reductions are included in CBA, they are usually valued as outcome-related productivity gains. Since the focus of this paper is on CBA, we assign mortality reductions, but not morbidity reductions, to the category "health gains".

tional achievements are related to labor productivity and income [35,36], these findings suggest that increased coverage of a vaccination that protects against common causes of meningitis can promote social well-being—a benefit that can potentially be measured and taken into account in CBA of vaccinations against Hib and other infections.

4.2. Behavior-related productivity gains

Broad-perspective economic analyses also account for gains in productivity that come about when vaccination effects change behavior. For instance, in areas with high child mortality rates, couples may choose to have more children in order to ensure the survival of a sufficient number of children who can work to support the family. As Hib vaccination can reduce child mortality, mothers of vaccinated children can achieve their target family size through fewer births. Having fewer children allows parents to invest more resources in each child, improving their nutrition, health, and educational attainment. These improvements, in turn, can increase a child's labor productivity as an adult.

At the population level, reductions in fertility rates will decrease the number of youth dependents relative to the size of the adult labor force, because fewer children are born and more women can participate in the labor market. A larger share of working-age individuals supporting a smaller number of children can lead to increased savings [37]. The additional savings can be used to invest in physical and human capital, stimulating economic growth. Research suggests that this phenomenon of rising shares of working-age people leading to increases in the rate of economic growth (the so-called demographic dividend [37,38]) contributed substantially to economic growth in the Republic of Ireland [39]

during the 1990s and in several East Asian nations since the mid-1960s [40,41].

4.3. Community externalities

In addition to outcome- and behavior-related productivity gains, community externalities are also often overlooked in economic analyses of vaccination. In the case of Hib vaccination, these include herd effects and reductions in antibiotic resistance. Herd effects are reductions in unvaccinated persons' risk of contracting a disease due to the vaccination of others [42]. Herd effects occur because vaccinated individuals will not contract and transmit a disease between infected and susceptible individuals, reducing disease transmission in a population [43,44]. A number of studies have documented marked reductions in the incidence of Hib infection [38,45–49] in unvaccinated persons, following the introduction of Hib vaccine into childhood immunization schedules. Herd effects can substantially affect the results of an economic evaluation of a vaccination, particularly in countries where large proportions of the unvaccinated population belong to groups that are at increased risk of either contracting a vaccine-preventable disease or developing severe forms of the disease, if they contract it. For example, the incidence of invasive Hib infection is substantially higher in HIV-infected than in HIV-uninfected individuals [50,51]. Thus, herd effects of Hib vaccination could imply large economic benefits in populations with high HIV prevalence among unvaccinated individuals.

Vaccination can lead to another type of community externality by avoiding the development of drug resistance. Many bacterial infections, including Hib infection, are treated with antibiotics. The probability of antibiotic resistance increases with the number of

patients treated with an antibiotic [52,53].⁵ In the case of Hib, infections with strains that are resistant to first-line antibiotics can be treated with second- and third-line antibiotics. However, these later-stage drugs may not be available in some settings and are far more costly than their first-line counterparts [55]. According to a recent study by Saha et al. [55], the proportion of cases of infection with Hib that are resistant to the first-line antibiotics ampicillin and chloramphenicol has risen to roughly 50% in some settings. Hib vaccination can prevent disease and thus obviate the need for antibiotic use, reducing the prevalence of antibiotic-resistant strains. This benefit is shared by communities, governments, and medical institutions, which might otherwise have to shoulder the morbidity burden, costs, and work load associated with treating antibiotic-resistant strains.

4.4. Broadening the perspective on benefits in cost–benefit analysis of Hib vaccination

All 11 studies identified by our review of CBA of Hib vaccination included benefits in the category ‘health-care cost savings’ (Table 3). Nine studies included benefits in the category ‘health gains’ and eight studies included benefits in the category ‘care-related productivity gains’. Only one study took the broad-perspective benefit ‘outcome-related productivity gains’ into account [56], and only one study incorporated the broad-perspective benefit ‘community externality’ in one of several CBA [57].

The BCRs of Hib vaccination estimated in the 11 studies ranged from 0.8 to 11.6. One study estimated a BCR below 1, five a BCR between 1 and 2, and four a BCR greater than 2. One study reported a positive net present value per vaccination [58], which is equivalent to a BCR greater than 1. Our argument that the scope of benefits accounted for in CBA of Hib should be broadened would not be relevant if we did not expect such broadening of the evaluation perspective to change decisions. If policymakers decided to implement any intervention with a BCR greater than 1, broadening the perspective could only change decisions based on two of the 11 studies in our set. Such a decision rule might seem plausible because in theory any intervention with a BCR greater than 1 will increase social well-being. However, in many cases a BCR that is not substantially larger than 1 (such as the six studies in this review with a BCR between 1 and 2) may not be sufficient to convince policymakers to adopt Hib vaccine into national immunization schedules.

First, policymakers usually face budget constraints, at least in the short-term. In this situation, social well-being will be maximized if interventions are ranked in decreasing order of BCR and the interventions with the highest BCRs are implemented until the budget is exhausted [59]. Broadening of the benefits that are taken into account in CBA will commonly increase the BCR rank of the vaccination and thus make it more likely that the vaccination is selected for implementation under such a decision rule. Even if policymakers do not use such a decision rule, we would expect them to generally prefer an intervention with a higher BCR over one with a lower BCR, when facing a budget constraint.

Second, in situations without budget constraints, policymakers might not implement an intervention with a BCR greater than 1, because they might not be convinced that all uncertainties have been captured adequately in the analysis and thus doubt the robustness of the finding. All else equal, we would expect that the larger

the estimated BCR the more likely policymakers will be to believe that the true BCR of the intervention is indeed greater than one. Thus, increases in the BCR of a vaccination should in many instances lead to changes in decisions regarding vaccine adoption, including in those cases where the BCR is already greater than 1.

It is important to note that seven of the eight CBAs of Hib vaccination that account for health gains, health-care cost savings, and care-related productivity gains state to have taken a “societal perspective” [56,57,60–62], a “societal point of view” [63], or a “social perspective” [58], or to have accounted for benefits and costs “to society as a whole” [26], while only one of the eight studies accounted for a broad-perspective benefit [56]. Thus, terms for perspectives of economic evaluations that seem to imply that all socially relevant benefits and costs are accounted for in the analysis in fact describe narrow evaluation perspectives (according to our definition of the term).

In general, we would expect studies that take a broader range of benefits into account to find BCRs that are more favorable than those using narrower ranges of benefits. For example, Levine et al. demonstrated in an analysis of infant vaccination with Hib in developing countries that the estimated health-related benefits of the vaccination increase when herd effects are taken into account (by 38%, measured in DALYs) [64]. It may thus seem surprising that the only study in our review that included a broad-perspective benefit is one of the two studies that found the Hib vaccination not to be cost-beneficial [56]. However, as Griffiths et al. have pointed out, the study used an inflated estimate of the cost of Hib vaccine (a public-sector price of US\$ 20 per dose, at a time when the vaccine was available for US\$ 9–11 per dose in the United States and for US\$ 8 per dose in Australia) [65]. In fact, a slightly lower cost estimate (US\$ 16 per dose) would have rendered the vaccination cost-beneficial in the study.

Bloom et al. [66] used standard life tables and relationships established in the literature among adult survival, adult height, and wages to estimate the return on investment (ROI) of a GAVI program to extend coverage of childhood vaccinations. They estimated that the vaccination program would have an ROI of 18% by 2020.⁶ In another analysis, Bloom et al. [67] used data from the Philippines’ Cebu Longitudinal Health and Nutritional Survey to estimate the effect of childhood vaccination on cognitive development. They found that vaccination significantly improved cognitive development as measured by language, mathematical, and non-verbal reasoning test scores. Translating cognitive gains due to childhood vaccination into adult income yields an ROI of 21%. These studies suggest that a proper accounting of the impact of vaccination requires an understanding of the broad scope of vaccine-mediated benefits. Ignoring the benefits of vaccination may lead to ill-informed decisions on vaccine adoption.

5. Rethinking the costs of Hib vaccination

Since 2000, total expenditures for routine vaccines in developing countries have risen. Expenditures have been projected to rise further in coming years as new vaccines are adopted into national immunization programs [68]. While narrow-perspective CBA of vaccinations may underestimate the benefits of Hib vaccination, they may also overstate its costs by failing to account for savings that can occur when vaccines are combined and delivered in a single vial as multivalent formulations. Many of the vaccination costs commonly included in CBA can be reduced when, instead of delivering a vaccine in single, monovalent form, it is

⁵ While antibiotic resistance is more likely to occur if patients do not adhere well to an antibiotic treatment regimen, antibiotic resistance can also develop in patients who adhere perfectly [54]. The general relationship between the number of patients receiving an antibiotic and resistance development thus holds, even if all patients were to adhere perfectly.

⁶ Education – considered by many to be one of the most important means of economic development – has ROIs of similar magnitude (ranging from 19% for primary education to 11% for tertiary education) [35].

Table 3
Cost–benefit analyses of Hib vaccination.

Study	Country	BCR or net benefits ^a	Assumed vaccination coverage (%)	Types of benefits considered	Number of vaccine doses	Valency of vaccine formulation
Asensi et al. [74]	Spain ^b	5.1 ^c	100	1 and 2	3	Monovalent
Garpenholt et al. [58]	Sweden	Net benefits per child: 160 SEK	99	1–3	3	Monovalent
Ginsberg et al. [26]	Israel	1.5	88	1–3	4	Monovalent
Jimenez et al. [57]	Spain	1.5 (1.2)	90	1–3 (2, 3, 5)	4	Monovalent
Lagos et al. [75]	Chile	1.1	100	2	3	Monovalent
Levine et al. [76]	Chile ^d	1.7	87	2	3	Monovalent
Limcangco et al. [60]	Philippines	11.6 ^c	85	1–3	3	Monovalent
Shin et al. [56]	Korea	0.8	90	1–4	3	Monovalent
Trollfors [77]	Sweden	2.8 ^c	100	1–3	3	Monovalent
Pokorn et al. [61]	Slovenia	1.4	95	1–3	3	Monovalent
Zhou et al. [62]	USA	5.4	93	1–3	3 and 4	Monovalent and multivalent

1 = health gains, 2 = health-care cost savings, 3 = care-related productivity gains, 4 = outcome-related productivity gains, 5 = community externalities (see Table 2 for definitions of these types of benefits). BCR = benefit–cost ratio.

^a All BCR estimates are rounded to the first decimal. When several BCR estimates were provided in the publication, we selected the largest BCR estimate available for the evaluation considering the largest set of benefits. If the BCR could not be calculated using data shown in the publication, we selected the net benefits as a summary measure of the CBA result.

^b Analysis was conducted at subnational level (Valencia).

^c BCR was calculated using data provided in the publication. The BCR for the 1995 article by Asensi et al. is based on the benefit estimate in Table 6 of the article (including the value of “loss of life”) and the cost estimate in the same table (for three-dose vaccination in the public sector) [74]. The BCR for the 2001 article by Limcangco et al. is based on the “total” benefit and cost estimates in Tables II and III of Ref. [60]. The BCR for the 1994 article by Trollfors is based on the “annual cost for hospitalization, neurologic and auditory sequelae and parents’ absence from work”, the “value of lives lost”, and the “vaccine costs” shown in the abstract of Ref. [77].

^d Analysis was conducted at subnational level (Santiago). SEK = Swedish Kronor.

added to an existing vaccine formulation and administered as a multivalent solution [68–73]. These costs include spending on the vaccine serum, syringes, cold chain storage, the health worker time required to administer the vaccination, and the costs of treatment of injection complications and adverse events.

For instance, the Hib vaccine can be delivered not only in monovalent form but also in combination with the trivalent DTP or the tetravalent DTP–HepB vaccine (i.e., as tetravalent DTP–Hib or pentavalent DTP–HepB–Hib vaccine, respectively). The pentavalent DTP–HepB–Hib vaccine is already being used in several countries and recommended for use by UNICEF, GAVI, WHO, and the Pan American Health Organization (PAHO) [69,78,79]. With one exception, all CBAs of Hib vaccination identified in our review estimate the value of adding the monovalent vaccine to current national immunization schedules (Table 3). However, the costs of adding the Hib vaccine in multivalent formulations to vaccines that are already delivered in the schedules will be lower than those of adding the monovalent Hib formulation. Using the lowest price estimates of DTP in the UNICEF/WHO 2009 *Immunization Summary* [78] and the lowest price estimates of Hib, DTP–Hib, and DTP–HepB–Hib in the UNICEF *Vaccine Projections for 2009* [80], adding a dose of monovalent Hib to an immunization program will cost US\$ 3.4, while the addition of Hib as part of the tetravalent formulation DTP–Hib will cost US\$ 3.1, and the addition of Hib as part of the pentavalent formulation DTP–HepB–Hib will cost US\$ 2.8.⁷

The above comparison considers merely the differences in prices of the Hib vaccine product. Comparing the costs of adding monovalent Hib vaccine to an existing immunization program with those of

adding the vaccine as part of tetravalent or pentavalent vaccine formulations further requires consideration of the costs of transport, storage, waste, and health worker time.

First, nearly all vaccines must be transported and stored in temperature-controlled conditions known as the cold chain storage network. This network constitutes a major implementation cost for all countries. Cold chain storage costs increase with vaccine volume. When using the lowest volume-per-dose estimate of Hib, DTP, DTP–Hib, and DTP–HepB–Hib listed in the WHO *Vaccine Volume Calculator* [81], the addition of one dose of monovalent Hib requires storage room for 3.3 cubic centimeters (cm³), while the addition of Hib in the tetravalent DTP–Hib requires no additional storage room and the addition of Hib in DTP–HepB–Hib requires additional storage room for only 0.6 cm³. Thus, the increase in cold chain costs will be substantially higher for adding monovalent Hib than for the addition of Hib in multivalent formulations.

A study of Ethiopia’s national vaccination services shows the size of the savings that can be achieved by combining vaccines into a single vial. The study found that cold chain storage costs alone accounted for over 75% of all system costs per fully vaccinated child, with a cost of US\$ 0.03 per additional cm³ of cold storage [82]. As the added volume required for storing the tetravalent DTP–Hib or the pentavalent DTP–HepB–Hib vaccines is less than that required for the monovalent Hib vaccine, using the pentavalent vaccine would be expected to significantly reduce system costs associated with cold chain storage relative to the use of the monovalent vaccine.

Second, it is immediately apparent that health worker time to administer vaccinations will be shorter if fewer injections are required. Furthermore, reducing the number of vaccine products will decrease the time healthcare managers need to spend organizing vaccine supply and storage. Administering Hib in a multivalent

⁷ The price estimates are weighted average prices across countries eligible for funding through GAVI [80].

formulation will thus be less time-consuming than administering it in its monovalent form.

Finally, disposing of biohazardous waste is expensive, often requiring costly incinerators,⁸ which can be particularly burdensome for developing countries. The costs of improperly disposing of the syringes and vials used in vaccinations may be even larger. These costs include infections due to needle-stick injuries, environmental degradation, and the emergence of social opposition to vaccination when syringes and needles are disposed of in publicly accessible places.⁹ Adding the Hib vaccine through use of the tetravalent or the pentavalent formulations implies that no syringes would need to be used in addition to those already in use for the DTP or the DTP–HepB three-shot vaccination series [84], averting the generation of additional hazardous waste.

5.1. Broadening the perspective on costs in cost–benefit analysis of Hib vaccination

None of the 11 studies in our review of CBA of Hib vaccination estimated the BCR when exclusively using pentavalent Hib formulations (Table 3); and only one [56] of the 11 studies considered cost reductions due to replacing the monovalent Hib vaccine with a combination vaccine. At baseline, the study estimated the BCR of Hib vaccination using the actual distribution of monovalent and multivalent Hib vaccines in the USA in 2000 (yielding a BCR of 5.4). In a sensitivity analysis the study then recalculated the BCR assuming that all Hib vaccinations were performed either with the monovalent formulation (yielding a BCR of 5.0) or with a HepB–Hib combination vaccine (yielding a BCR of 7.5). This example demonstrates the increase in estimates of vaccination value if multivalent formulations are used in evaluation as opposed to monovalent vaccines. It is likely that all studies listed in Table 3 would have found substantially higher BCRs had they evaluated the tetravalent DTP–Hib or the pentavalent DTP–HepB–Hib vaccine instead of the monovalent Hib form.

6. Discussion

Past economic evaluations of vaccinations have usually ignored both important benefits and potentially large cost reductions and may thus have substantially underestimated the value of vaccinations. We demonstrate, for the example of the Hib vaccination, that CBAs have taken narrow evaluation perspectives, focusing on health gains, health-care cost savings, and care-related productivity gains, while usually ignoring other benefits, in particular, outcome-related productivity gains, behavior-related productivity gains, and community externalities.

At the same time, the economic evaluations have also usually ignored savings that can be achieved if economies of scope in vaccination delivery are fully exploited. We show for the example of

the Hib vaccine that substantial cost reductions are likely to occur if a monovalent Hib formulation is replaced by a combination vaccine, because adding the Hib vaccine to an immunization schedule in a multivalent form reduces the costs of serum, storage, health worker time, and hazardous waste.

Theoretically, combination vaccines may have a few disadvantages. For instance, if only combination vaccines are available in a country, some children may unnecessarily forgo the opportunity to receive some vaccinations because they have a medical contraindication against one specific vaccine included in the combination. This potential problem, however, may not affect a large number of children and can be avoided using combination vaccines in routine situations but offering children with vaccine-specific contraindications those vaccines they can safely receive in monovalent forms.

Our analysis suggests that past CBAs of Hib vaccination have underestimated the net value of the vaccination, even though most have found it to be cost-beneficial. One hundred and sixty countries either introduced the Hib vaccine by 2009 or are expected to introduce it in 2010. Nevertheless, global Hib vaccination coverage in the target population of children less than one year of age remains low (28% in 2008 [6]). Our results should encourage researchers to conduct CBA of Hib vaccination that take into account broad sets of benefits and costs. This new approach may also be of interest to researchers investigating the economic value of other existing childhood vaccinations, such as rotavirus vaccination [85–87], and to scientists studying the economics of investment in the discovery of new vaccines and the development of new vaccination delivery systems [88].

Our arguments are of course only relevant for policy insofar as results of economic evaluations enter into political decision-making. While some early evidence suggests that economic evaluations are rarely used systematically in health policymaking [89], more recent research suggests a somewhat more optimistic picture, e.g., that “[d]ecision makers generally recognized the usefulness and necessity of published economic evaluations in informing their decision-making processes” [90]. In some countries, economic evaluations are systematically included in the decision-making regarding the delivery of health interventions in the public-sector health-care system. For instance, the United Kingdom’s National Institute for Health and Clinical Excellence (NICE), which provides “guidance on the use of new and existing medicines, treatments and procedures within the NHS [the UK National Health Service]” [91], systematically incorporates evidence from economic evaluations of health interventions in issuing recommendations for health policy, including guidance on the adoption of new vaccines into the national immunization schedule [92]. In the particular case of decisions on the introduction of relatively expensive vaccines, it has been noted that policymakers’ reluctance to commit to financing the inclusion of the vaccine into national immunization schedules can be reduced by evidence of substantial long-term economic benefits of the vaccination [93].

In addition, it is plausible that the results of economic evaluation enter the policymaking process indirectly, as they contribute to a general understanding – conveyed formally by policy advisors or informally in meetings and discussions among policymakers, scientists, and advocates – as to whether an intervention is “good value” for government budget money. It is important that obstacles to the use of economic evaluation in policymaking are better understood and, where possible, removed, such as through better communication of relevant findings [94].

A number of caveats are important to keep in mind when considering our approach to expanding the perspective of economic evaluation of vaccination. For one, the different benefits and costs included in broad-perspective evaluations of vaccinations accrue

⁸ Of course, the fixed costs of incinerators and other infrastructure to dispose of biohazardous waste need to be allocated across all products that are disposed of using this infrastructure. The fraction of total fixed costs allocated to the Hib vaccine is likely to be small.

⁹ For instance, WHO estimates for 2000 identify contaminated syringes and needles as the cause of 32% of all new hepatitis B infections, 40% of all new hepatitis C infections, and 5% of all new HIV infections, resulting in significant morbidity, mortality, and monetary costs for individuals and society. This is a particular issue in developing countries as few have established systems for managing sharps waste. In remote and rural areas of developing countries, the combination of poor road conditions and personnel reluctant to transport the unwieldy and hazardous waste contributes to inappropriate and unsafe disposal, often through shallow burial or open burning. Urban areas face similar problems because primary health clinics rarely have access to hospitals’ incinerators and thus dispose of sharp waste in public waste sites, leading to injury and infection, or through open burning, which is often toxic [83].

at different times relative to the date of vaccination. For instance, the timing of health gains will depend on the disease avoided by the vaccination—some diseases, such as measles, will mostly affect children, while others, such as hepatitis B, substantially affect both children and adults and thus lead to health gains throughout the life course. Outcome-related productivity gains will usually start accruing only once the individuals vaccinated as children enter the labor market. Behavior-related productivity gains may materialize only after long lags because changes in child health and survival may first need to be observed in children already born before they can change future fertility decisions. Cost reductions due to changes in vaccine formulation, on the other hand, will be realized immediately at the time of the vaccination. Because the broad-perspective evaluation expands the sets of benefits and costs included in the analysis, the relative timing of benefit and cost realization will be more complex than in narrow-perspective studies.

Broader evaluation perspectives may also require more complicated methodologies than narrower perspectives. For instance, in order to incorporate the community externality of herd effects into an economic evaluation of vaccination, researchers may need to employ dynamic models instead of the standard static models [95]. In static models, vaccination is assumed to reduce the number of individuals susceptible to a vaccine-preventable disease but not to alter the infection rate acting on those who remain susceptible because they have not received the vaccination. Dynamic models that take account of herd effects are more complex because they relax the assumption of a constant infection rate. Instead, they assume that the infection rate is a function of the number of infectious individuals in the population at a given point in time, the contact rate between susceptible and infectious individuals, and the probability of transmission per contact [96]. This added complexity allows dynamic models to estimate both the direct vaccination effect of decreasing the size of the susceptible population and the herd effect, which occurs because vaccination results in fewer infectious individuals in the population and thus in a lower infection rate among the unvaccinated. Dynamic models are still rarely used [97] in the economic valuation of vaccination, although they are emerging in the literature [98–101].

Additionally, broader evaluation perspectives may require more extensive data collection. For example, analysis of the economic effects of vaccination on antibiotic resistance will require information that may not be currently available, such as data on the speed of resistance development at different levels of vaccination coverage and disease incidence. Increased data requirements and greater demands on the skills of the evaluator conducting the analysis, however, should not distract from the fact that broad-perspective evaluations of vaccinations will improve the validity of evaluation results and should thus be undertaken whenever feasible.

Understanding the complex relationships among health interventions, health outcomes, education, and labor productivity has implications for all types of interventions, not only childhood vaccinations. However, evidence on the “broad” benefits of many health interventions is largely lacking. For instance, we know little about the links between many specific childhood vaccinations and cognition and educational attainment. Future research must seek to fill these knowledge gaps in order to improve the specificity of recommendations to include certain types of “broad” benefits in the economic evaluation of individual health interventions. In planning such research, it is important to keep in mind that research itself has benefits and costs—in some situations, the expected marginal benefits of broadening the evaluation perspective may not exceed the marginal costs of the study. This will be the case in particular where additional information is unlikely to change a decision. Consider, for instance, a health intervention that has been found to

be highly cost-beneficial in narrow-perspective evaluations. If we know based on theoretical considerations, such as those described in this paper, that the estimates of the benefits of the intervention are a lower bound of the true benefits, the value of the additional information to be gained in broad-perspective evaluation may not exceed the costs of the study.

One type of broadening of evaluation perspective that is not considered above relates to the possibility that the children who would be vaccinated if vaccination coverage were to be expanded in a country, stand to benefit more from vaccination than children who were vaccinated in the past. A number of studies suggest that children who reside farther away from clinics, who come from households of lower socioeconomic status, or whose mothers have fewer years of education, are less likely to receive vaccinations [102–106]. Children with these characteristics are also more likely to suffer if they contract a vaccine-preventable disease than children who live in more privileged circumstances, because they will be less likely to have access to health-care and to support systems that can reduce the effect of disease sequelae on their lives. At the same time, it is likely that the marginal costs of extending vaccination coverage to additional children are increasing. Past economic evaluations have usually assumed that the vaccination benefits and costs observed in vaccinated children are valid for those children who are currently unvaccinated. Future CBAs of Hib and other vaccinations should take into account that both the costs and the benefits of a vaccination may change as coverage increases, possibly leading to different overall estimates of vaccination BCR.

A final caveat for conducting CBA of vaccinations relates to the choice of vaccine costs in the analysis. Prices that are subsidized by international or national donors [107] should not be used to estimate the costs of vaccines in all types of evaluations. From a societal perspective, subsidized prices will underestimate the true market costs of producing the vaccines and should thus be replaced with “shadow prices” that adequately represent the opportunity costs to society of producing vaccines [108]. From the perspective of a Ministry of Health, a subsidized price may be relevant for short-term planning purposes [107], but planners must consider that subsidies are usually temporary and prices will revert back to their true market values after some time.

Vaccinations can save the lives of millions of children. Improved vaccination coverage can thus clearly contribute to the progress towards the fourth Millennium Development Goal (MDG) of reducing child mortality. Broad-perspective economic evaluation can draw attention to the non-health benefits of vaccination, including effects on educational attainment (which are relevant for the second MDG of achieving universal primary education) and labor productivity (which is relevant for the first MDG of eradicating extreme poverty and hunger). Only when all benefits of vaccinations for health, education, and the economy of a country are known and considered simultaneously with the cost of vaccine delivery will policymakers be able to make well-informed decisions regarding vaccinations.

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